IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

HUBBELL, et al.

Serial No.: 08/783,387

Filed: January 13, 1997

For: GELS FOR ENCAPSULATION OF BIOLOGICAL MATERIALS

Group Art Unit: 1507

Examiner: S. Berman

DECLARATION OF CAROL A. SCHNEIDER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

1. I, Carol A. Schneider, a citizen of the United States, hereby declare that:

2. I am registered to practice at the United States Patent and Trademark Office, Registration Number 34,923. I am also named on the Power of Attorney for application Serial No. 08/783,387 ("the '387 application").

3. I am prosecuting the '387 application on behalf of its owner, The Regents, University of Texas, and its licensees, including Novocell Inc. (formerly Neocrin Company) ("Novocell").

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Rick Moreno
Name of Person Mailing Paper

November 12, 1999
Date of Deposit

Rick Moreno
Signature of Person Mailing Paper

4. I have been involved in the preparation of a Declaration under 37 CFR § 1.131 ("Rule 131 Declaration") with respect to the '387 application. In particular I have attempted to obtain the signature on the Rule 131 Declaration of one of the named inventors--Neil Desai.

5. Desai is currently employed by American Pharmaceutical Partners, a company related to VivoRx, Inc. ("VivoRx"). VivoRx is a direct competitor of Novocell and has no rights in the '387 application.

6. On or around May 18, 1999, I contacted Desai and requested that he read papers from the prosecution file for the '387 application, including the Preliminary Amendment filed April 8, 1997, adding claims 129-188, the Amendment and Response dated December 1, 1997, including amendments to the claims, the Preliminary Amendment (for the CPA application) filed September 16, 1998, adding claim 190, and the Office Action dated November 18, 1998. These papers show the claims in the '387 application and how they had been amended, and the then-current rejections. I also requested that he read and sign the Rule 131 Declaration.

7. Desai responded to this request by refusing to sign the document without first being allowed to show the documents to "my lawyers." I asked him whether he meant the patent lawyers for VivoRx when he used the term "my lawyers," and he replied yes. As this would be disclosing confidential information belonging to Novocell to its direct rival, I informed him that such a disclosure would be unreasonable and unacceptable.

8. On October 12, 1999, I again contacted Desai, this time by telephone, and asked him if he would read the papers and sign the Rule 131 Declaration. He again refused unless he was able to show them to the VivoRx lawyers.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: November 12, 1999

Carol A. Schneider

Carol A. Schneider
Reg. No. 34,923

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Group Art Unit: 1507

Examiner: S. Berman

DECLARATION UNDER 37 C.F.R. §1.131

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

1. We, Jeffrey A. Hubbell, a citizen of the United States, Chandrashekhar P. Pathak, Amarpreet S. Sawhney and Neil P. Desai, each citizens of India, and Syed F.A. Hossainy, a citizen of Bangladesh, hereby declare that:

2. Our addresses are Institute for Biomedical Engineering and Department of Materials, Swiss Federal Institute of Technology (ETH) Zurich and University of Zurich, Moussonstrasse 18, CH-8044 Zurich Switzerland; 4300 Tandem Boulevard, No. 175, Austin, Texas 78728; 164 Springs Road, Bedford, Massachusetts 01730; 3633 Purdue Ave., Los

CERTIFICATE OF MAILING (37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

November 12, 1999

Rick Moreno

Rick Moreno

Angeles, California 90066, and Route 22 West, P.O. Box 151, Somerville, New Jersey 08876, respectively.

3. We are the named co-inventors of the subject matter of this invention which claims benefit of the February 28, 1992 filing date of U.S. Application Serial No. 07/843,485, now abandoned ("Priority Document 1") of which four of us (Hubbell, Pathak, Sawhney and Desai) are also co-inventors. The four co-inventors listed in the immediately preceding sentence are also co-inventors of U.S. Application Serial No. 07/870,540, filed April 20, 1992, now abandoned ("Priority Document 2") which is a continuation-in-part of Priority Document 1.

4. We understand that the Examiner has cited Soon-Shiong et al., U.S. Pat. No. 5,700,848 ("Soon-Shiong '848") in his rejection of the certain claims presented in our present application (the "Application"). We also understand that Soon-Shiong '848 has an effective filing date of October 29, 1991. Before Soon-Shiong '848 was filed, we reduced to practice in the United States a method of microencapsulating biological materials which comprises mixing the biological material with an aqueous macromer solution and a photoinitiator, generating microcapsules and polymerizing the gel using a light source in accordance with the subject matter claimed in this application.

5. Our disclosure of several microencapsulation methods appears in the Application at page 10, line 23 through page 11, line 4, and at page 12, line 16 through page 13, line 14. One method is the bulk suspension polymerization method that is the subject of our claim 129 and claims 130-163 that depend on it and is the method cited in the Examiner's

rejection as anticipated by Soon-Shiong '848. (See Application page 13, line 9. This method is also described in Priority Document 1 page 26, lines 7-15; and Priority Document 2 page 20, lines 8-21.)

6. Prior to October 29, 1991, we completed our invention of the method of bulk suspension polymerization in our laboratory in Austin, Texas. A copy of the pertinent sequential pages from the bound laboratory notebook of Chandrashekhar P. Pathak is attached to this Declaration as Exhibit 1. Exhibit 1, page 1 describes the completion of our invention. Other details appear on the pages of Exhibit 1 that follow. Except for the masked dates, Exhibit 1 is a true and correct copy of the relevant pages in their original order in the original bound laboratory notebook. Pages 3 and 4 of Exhibit 1 bear dates earlier than October 29, 1991. Because it was the custom and practice of Chandrashekhar P. Pathak to record data in his notebook on pages in sequential order, pages 1 and 2 of Exhibit 1, while not themselves dated, described our laboratory work which occurred before the dates shown on pages 3 and 4 of Exhibit 1. Exhibit 2 is our transcription of portions of Exhibit 1.

7. Exhibit 1, page 1 describes a phosphate buffered saline ("PBS") solution of poly(ethylene oxide) ("PEO"), ethyl eosin ("EE") and triethanolamine ("TEA") suspended in oil that is irradiated at 514 nm with an argon laser, which causes the solution to polymerize into beads. The beads are removed under sterile conditions and are sieved through a 45μL filter to remove the larger particles. The gel beads are then incorporated into mice and later recovered. Exhibit 1, page 4 shows a similar process used to encapsulate beta cells of the insuloma line (RiN5F).

8. The terms and methods used in Exhibit 1 are supported in the Application and in the Priority Documents and can be seen to include the same steps as required by claim 129. PEO of Exhibit 1 is a species of the macromer of claim 129 (Application, page 21, lines 1-2; Priority Document 1, page 26, lines 33-35; Priority Document 2, page 18, lines 11-13) that is described as water soluble (Application, page 20, lines 27-28; Priority Document 1, page 26, lines 33-35; Priority Document 2, page 18, lines 11-13). Exhibit 1 shows PEO dissolved in PBS, a saline solution, thus forming an aqueous macromer solution as required by claim 129. The Application describes eosin dye as the preferred photoinitiator (Application, page 12, line 23), and more particularly, ethyl eosin (Application, page 22, lines 13-14; Priority Document 1, page 27, lines 12-13; Priority Document 2, page 19, lines 4-14) which is used in the method described in Exhibit 1. As further described in Exhibit 1, ethyl eosin is mixed with the PEO solution and beta insuloma cells as required by the first step of claim 129. Triethanolamine described in Exhibit 1 is an optional co-catalyst that stimulates the free-radical polymerization reaction (Application, page 12, lines 28-29.) The co-catalyst is described in Priority Document 2 at page 19, lines 14-23, and its optional inclusion in the method is described at page 20, lines 13-14 and in Priority Document 1 page 27 at lines 11-12. The Application describes the required radiation for polymerization as either visible or long wave ultraviolet light which is nontoxic to biological materials (Application, page 10, lines 27-29 and page 11, lines 26-29; Priority Document 1, page 34, lines 9-11 and lines 22-25; Priority Document 2, page 12, lines 5-8 and lines 22-25). The Application further describes the most preferred wavelength as 365-514 nm (Application

page 13, lines 4-5; Priority Document 1, page 27, lines 15-17; Priority Document 2, page 19, lines 23-24) and states that an appropriate source is an argon ion laser (Application page 23, lines 6-8; Priority Document 1, page 34, lines 31-34; Priority Document 2, page 29, lines 3-5). Exhibit 1 states that the above-described aqueous macromer solution containing biological material is irradiated with a "514 Argon ion laser, polymerized and beads were removed." Exhibit 1, p.1 states that the product of the above-described process is incorporated in mice. More specifically, Exhibit 1, page 4 shows this type of process used to encapsulate RiN5F cells, which the Application describes as beta cells of the insuloma line (Application, page 34, line 19; Priority Document 2, page 31, line 18-22.) Thus, Exhibit 1 carries out the steps of claim 129, where an aqueous macromer solution and a photoinitiator are mixed with biological material consisting of mammalian tissue or mammalian cells and the macromer is polymerized by its exposure light radiation between 320 nm and 900 nm. The original pages of Exhibit 1, pages 3 and 4 bear dates prior to October 29, 1991, and Exhibit 1, pages 1 and 2 appear before page 3 in the bound laboratory notebook.

9. Accordingly, Exhibit 1 demonstrates that we completed our invention as described in claim 129 in the Application before the filing date of Soon-Shiong '848.

10. We understand that the Examiner has also cited Soon-Shiong et al., U.S. Pat. No. 5,545,423 ("Soon-Shiong '423") in her rejection of the claims presented in our Application. We understand that the Soon-Shiong '423 patent has an effective filing date of November 25, 1991, which is later than Soon-Shiong '848. Therefore, as shown above, we

completed our invention as described in claim 129 before the effective filing date of Soon-Shiong '423.

11. We understand that the Examiner has also cited Desai et al. U.S. Pat. No. 5,334,640 ("Desai '640") in her rejection of the claims presented in our application. We understand that Desai '640 has an effective filing date of April 8, 1992, which is later than Soon-Shiong '848. Therefore, as shown above, we completed our invention as described in claim 129 before the effective filing date of Desai '640.

12. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 14 June 1999

Jeffrey A. Hubbell

12. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 06/09/99

Chandrashekhar P. Pathak

12. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 5/18/99

Amarpreet S. Sawhney

12. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: _____ _____

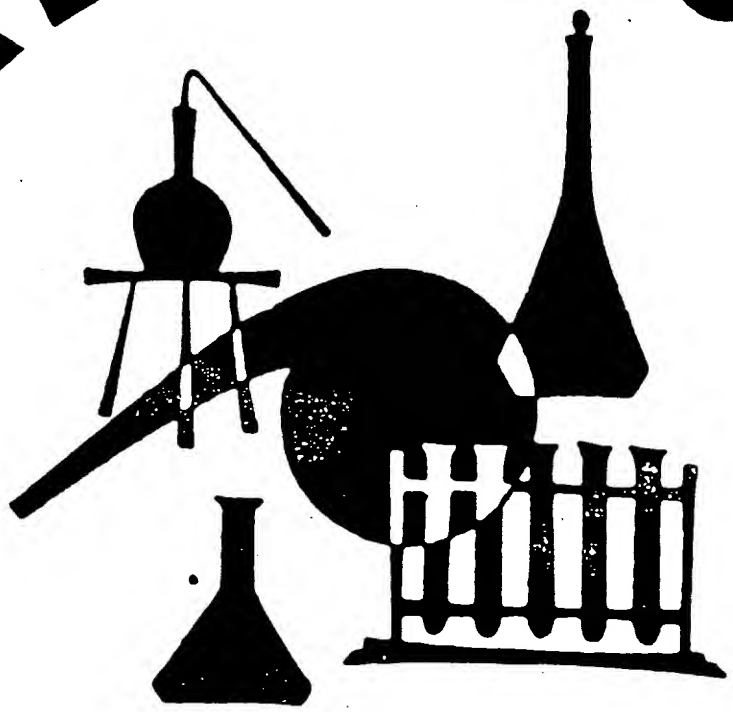
Neil P. Desai

12. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 10/26/99

Syed F.A. Hossainy

LABORATORY



NOTEBOOK

COURSE _____

NAME _____

PERFORATED SHEETS
DUPLICATING WITH
CARBON

Comet
3-0207

100 SHEETS—50 SETS 11 IN. X 8½ IN.

COMET SCHOOL SUPPLIES • PALESTINE, TEXAS 75801

NAME EXPERIMENT NO. DATE

PEO, 5000

20 gm of 5K PEO =

20 % 5K solution in ~~PEO~~ PBS buffer
10 % 18.5K soln in PBS buffer.

(1ml)
~~10 ml~~ 5K solution and 1 ml of above solutions (5K and 18.5K 1 ml each) were irradiated at 514 argon ion laser in sterile paraffin oil. ~~The~~ Cinthalin system ~~is~~ Ethyl eosin 10^{-4} M and Triethanol amine = 0.1 M. The suspension was irradiated polymerized and beads were removed all under sterile conditions.) (note: The mixtures of solutions was filtered with 45 μ filter to make it sterile. Hexane and paraffin oil were also sterilized by filtration.

The beades were seived (size NO. ... the only one we have) to remove bigger size gel particals. These gels were interpreted in mine. (Amar's help is appreciated)

After 4 days, ~~5K beads were covered~~ both beads were recovered. with this observation.

5K beads — completely covered with cells

5K + 18.5K → total ml = 2 ml ratio of 5K : 18.5K is (2 : 1)
20% soln. 20% soln means 33⅓ % 18.5K beads were

on lysine
- 5K : 18.5K
- 0.4K : 18.5K

- 5K : 18.5K (5K 20%) → solid spheres
- 5K : 18.5K
- 0.4K : 18.5K (lysine)

NAME EXPERIMENT NO. DATE.

5K

Protein wavelength dye solution was prepared by diluting bicinchoninic protein assay solution (1 volume of dye with 4 volume of water) and solution was filtered with glass wool.

10 mg of hemoglobin, egg albumin were weighed in 10 ml. 1 ml of PBS was added to each bottle and left overnight. plastic bottles. To each solution 1 ml of PEO 5K solution (conc. 200 mg/ml) 20 microliter Ethyl eosin (5 mg/ml in vinyl pyrrolidone), Two drops of triethanol amine (1 drop = 15 to 18 mg) and PEO 1000 dicrylate was added ( ). The solutions were mixed and irradiated. The solutions were irradiated to mercury lamp (with u.v. cutoff filter) for 2 to 3 minutes) and gelled. These clear gels were with 5 ml of PBS buffer and washing was discarded. The 5 ml of PBS was added. The 200 is all was taken out from each bottle and then mixed with 5 ml of bicinchoninic solution. (The amount of solution removed from analysis was replaced with PBS buffer).

The absorbance of resulting solution was measured.

Similarly the calibration of albumin and fibrinogen

EXPERIMENT NO. DATE

RNFIS, insulinoma cell line cells were recently obtained. The original cell culture had viability ≈ 70-80%. These cells are kept for culture.

1 million cells were suspended in 1 ml medium and this solution was used to check viability.

1 ml of 30% 12-strand DNA in silane + 0.4 ml PBS buffer + 200 µl of TEA solution + 10 µl of dye (EE in VP 5 mg/ml) + 50 µl of cell suspension. mixed and irradiated using argon laser. power ≈ 500 mW, beam expanded 4 mm diameter

Estimates about time scale of irradiation

solution: PEO 400 diacrylate ≈ 3 ml neat liquid
200 µl of EE soln in VP (EE = 5 mg/ml) (2 drops =)
50 drops of 50% TEA solution in silane

Exposure time = 1 sec.
Gel formed ≈ 3 mm

(Power used is minimum on Argon ion laser ≈ 60 mW
gel diameter ≈ 4 mm at bottom

This gives 3000 µ micron gel formed in 1000 millisecond. ∴ 3 microns gel formed in 1 millisecond

it means it takes about 100 millisecond exposure time to gel this particular solution.

PEO in water forms a gel but that is difficult to measure because it is too weak to withstand its own weight.

At higher powers of laser, polymerization time will be even slower.

EXHIBIT 2

Transcription of handwriting of Exhibit 1, page 1

PEO , 5000[1]
20 gm of 5K[2] PEO

20% 5K solution in PBS[3] buffer
10% 18.5 solu[tion] in PBS buffer

5K solution (1m) ≈ 1 1ml of above solutions (5K and 18.5K 1 ml each) were irradiated at 514[4] argon ion laser in sterile paraffin oil. (initialy system is ethyl eosin 154(?) M and Triethanol amine = 0.1M. The suspension was irradiated, polymerized and beads were removed all under sterile conditions.) (note: The mixtures of solutions were filtered w/ 45 μ liter to make it sterile. hexane and paraffin oil were also sterilized by filtration.

The beads were seived (size No ..., the only one we have) to remove bigger size get particals

These gels were incorporated in mice. (Amar's help is appreciated.)

After 4 days, both beads were recovered with this observation.

5K beads - completely covered with cells

5K	+ 18.5K	→ total ml = 2ml ratio of 5K:18.5K is (2:1)
20% solution	20% solution	means 33 1/3% 18.5K beads were

[1] "PEO" is poly (ethylene oxide). "PEO 5000" is PEO with molecular weight of 5000.
[2] "K" means kD, or kiloDalton.
[3] "PBS" is phosphate buffered saline.
[4] "514" means 514 nm, the wavelength of the argon laser.

EXHIBIT 2

Transcription of handwriting of Exhibit 1, page 4 (top two paragraphs)

RNF15[5], insuloma cell line cells were recently obtained. The original cell culture had viability ≈ 70 to 80 %. These cells are kept for culture.

1 million cells were suspended 10 ml medium and this solution was used to check ciability.

1 mil 30% 18.5k DA in silane[6] + 0.6 ml PBS buffer + 200 µl of TEA[7] solun + 10µl of dye (EE[8] in UP 5 mg/ml) + 50µl of cell suspension. mixed and irradiated using argon laser. power ≈ 500 wt, beam expanded 4 mm diameter

[*Bottom section of page with new date*]

Estimates about time scale of irradiation

solution: PEO 400 diacrylate ≈ 3 ml neat liquid
20µl of EE solun in UP (EE = 5 mg/ml) (2 drops)
50 drops of 50% TEA solution in silane [see footnote 6]

Exposure time ≈ 1 sec.
Gel formed ≈3 mm (power used is minimum on Argon ion laser ≈ 60 mw)
gel diameter ≈ 1 mm at bottom.

This gives 3000 micron gel forms in 1000 milisecond. ∴ 3 microns gel formed in 1 millisecond it means it takes about 100 millisecond exposure time to gel this particular solution.

PEO in water forms ≈ gel but that is difficult to measure because it is too weak to withstand its own weight. At higher powers of laser, polymerization time will be even slower.

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[5] "RNF15" means RiN5F, a beta cell insuloma line.
[6] Incorrect spelling of "saline".
[7] "TEA" is triethanolamine.
[8] "EE" means ethyl eosin.